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SCREENING OF PSYCHOTIC PATIENTS FOR THE SCHIZOPHRENIFORM VARIANT OF NARCOLEPSY

by

© STANISLAW TEOFIL MLYNCZAK

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF PSYCHIATRY

EDMONTON, ALBERTA

SPRING, 1993

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TABLE I: NREM AND REM SLEEP CHARACTERISTICS IN MAN

Measurement	*NREM Sleep*	*REM Sleep*
Scalp EEG	Slow waves and spindles	Low voltage, mixed frequency
Hippocampal EEG	Variable	Rhythmic theta activity
Eye movements	None or few slow movements	Conjugate rapid movements
Chin EMG	Decreased from wakefulness	Almost absent
Body movements	A few gross movements	Twitches
Respiration	Regular, deep	Variable, shallow
Heart rate	Regular, slow	Variable, rapid
Blood pressure	Below waking level	Variable
Penile erection	Absent	Present
Mentation	Thought-like, repetitive	Dream-like, dramatic
Galvanic skin response	Frequent	Rare

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to detailed scrutiny: crucially, many patients had become psychotic before stimulants were used (personal communication with Dr. P. Hays).

TABLE II:

Frequency of symptoms in 111 schizophrenic patients

Symptom	%	Symptom	%
NEGATIVE SYMPTOMS		POSITIVE SYMPTOMS	
• Affective flattening		• Hallucinations	
Unchanging facial expression	98	Auditory	75
Decreased spontaneous movements	66	Voices commenting	58
Paucity of expressive gestures	61	Voices conversing	57
Poor eye contact	71	Somatic-tactile	20
Affective nonresponsivity	64	Olfactory	6
Inappropriate affect	63	Visual	49
Lack of vocal inflections	73		
		• Delusions	
• Alogia		Persecutory	81
Poverty of speech	53	Jealous	4
Poverty of content of speech	51	Guilt, sin	26
Blocking	23	Grandiose	39
Increased response latency	31	Religious	31
		Somatic	28
• Avolition-apathy		Delusions of reference	49
Impaired grooming and hygiene	87	Delusions of being controlled	46
Lack of persistence at work or school	95	Delusions of mind reading	48
Physical anergia	82	Thought broadcasting	23
		Thought insertion	31
• Anhedonia-asociality		Thought withdrawal	27
Few recreational interests/activities	95		
Little sexual interest/activity	69	• Bizarre behavior	
Impaired intimacy/closeness	84	Clothing, appearance	20
Few relationships with friends/peers	96	Social, sexual behavior	33
		Aggressive-agitated	27
• Attention		Repetitive-stereotyped	28
Social inattentiveness	78		
Inattentiveness during testing	64	• Positive formal thought disorder	
		Derailment	45
		Tangentiality	50
		Incoherence	23
		Illogicality	23
		Circumstantiality	35
		Pressure of speech	24
		Distractible speech	23
		Clanging	3

Source. Adapted from Andreasen NC: The diagnosis of schizophrenia. Schizophr Bull 13:9–22, 1987

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TABLE III: DSM-III-R CRITERIA FOR SCHIZOPHRENIA

(A) Presence of characteristic psychotic symptoms in the active phase: either (1), (2) or (3) for at least 1 week (unless symptoms are successfully treated):

(1) Two of the following:

a. delusions

b. prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments)

c. incoherence or marked loosening of associations

d. catatonic behaviour

e. flat or grossly inappropriate affect

(2) Bizarre delusions (i.e. involving a phenomenon that the person's culture would regard as totally implausible, e.g. thought broadcasting, being controlled by a dead person).

(3) Prominent hallucinations [as defined in (1b) above] of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behaviour or thoughts of two or more voice conversing with each other.

(B) During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved before onset of the disturbance (or, when the onset is in childhood or adolescence, failure to achieve expected level of social development).

(C) Schizoaffective disorder and mood disorder with psychotic features have been ruled out; i.e., if a major depressive or manic syndrome has ever been present during an active phase of the disturbance, the total duration of all episodes of a mood syndrome has been brief relative to the total duration of the active and residual phases of the disturbance.

(D) Continuous signs of the disturbance for at least 6 months. The 6-month period must include an active phase (of at least 1 week, or less if symptoms have been successfully treated) during which there were

psychotic symptoms characteristic of schizophrenia [symptoms in (A) above], with or without a prodromal or residual phase, as defined below.

Prodromal phase: A clear deterioration in functioning before the active phase of the disturbance that is not due to a disturbance in mood or to a psychoactive substance use disorder and that involves at least two of the symptoms listed below.

Residual phase: Following the active phase of the disturbance, persistence of at least two of the symptoms noted below, those not being due to a disturbance in mood or to a psychoactive substance use disorder.

Prodromal or residual symptoms:

1. Marked social isolation or withdrawal.
2. Marked impairment in role functioning as wage earner, student or homemaker.
3. Marked peculiar behaviour (e.g., collecting garbage, talking to self in public, hoarding food).
4. Marked impairment in personal hygiene and grooming.
5. Blunted or inappropriate affect.
6. Digressive, vague, overelaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech.
7. Odd beliefs or magical thinking, influencing behaviour and inconsistent with cultural norms, e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense", "others can feel my feelings", overvalued ideas, ideas of reference.
8. Unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present.
9. Marked lack of initiative, interests, or energy.

Examples: Six months of prodromal symptoms with 1 week of symptoms from (A); no prodromal symptoms with 6 months of symptoms from (A); no prodromal symptoms with 1 week of symptoms from (A) and 6 months of residual symptoms.

(E) It cannot be established that an organic factor initiated and maintained the disturbance.

(F) If there is a history of autistic disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present.

Classification of Course: The course of the disturbance is coded in the fifth digit:

1 - Subchronic. The time from the beginning of the disturbance, when the person first began to show signs of the disturbance (including prodromal, active, and residual phase) more or less continuously, is less than 2 years, but at least 6 months.

2 - Chronic. Same as above, but more than 2 years.

3 - Subchronic with acute exacerbation. Reemergence of prominent psychotic symptoms in a person with a subchronic course who has been in the residual phase of the disturbance.

4 - Chronic with acute exacerbation. Reemergence of prominent psychotic symptoms in a person with a chronic course who has been in the residual phase of the disturbance.

5 - In remission. When a person with a history of schizophrenia is free of all signs of the disturbance (whether or not on medication), "in remission" should be coded. Differentiating schizophrenia in remission from no mental disorder requires consideration of overall level of functioning, length of time since the last episode of disturbance, total duration of the disturbance, and whether prophylactic treatment is being given.

0 - Unspecified.

[from Andreasen and Black (1991) *Introductory Textbook of Psychiatry*, American Psychiatric Press, Washington, D.C. Original source: American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, American Psychiatric Association, Washington, D.C.].

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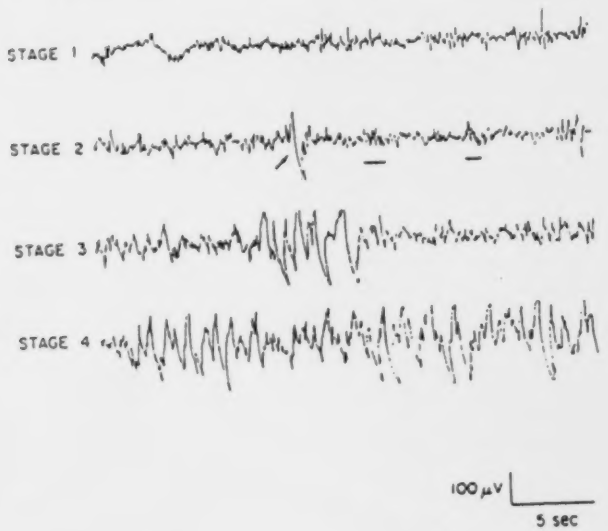

Figure I: The stages of NREM sleep. The four electroencephalographic (EEG) tracings depicted here are from a 19-year old female volunteer. Each tracing was recorded from a referential lead (C3/A2) recorded on a Grass Instruments Co. Model 7D polygraph with a paper speed of 10 mm/sec, time constant of 0.3 sec, and 1/2 amplitude high-frequency setting of 30 Hz. On the second tracing, the arrow indicates a K complex, and the underlining shows two sleep spindles. [From Kryger *et al.* (1989) In: *Principles and Practice of Sleep Medicine*, W.B. Saunders Co., Philadephia, PA].

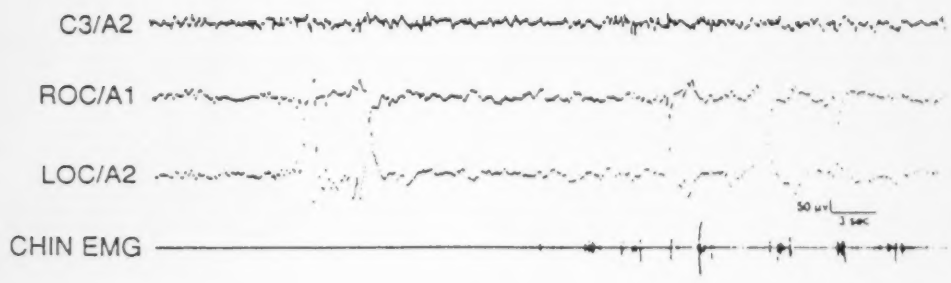

Figure II: REM sleep. Phasic events in human REM sleep are illustrated in this figure. On the left side is a burst of several rapid eye movements (out-of-phase deflections in ROC/A1 and LOC/A2). On the right side, there are additional rapid eye movements as well as twitches on the electromyographic (EMG) lead. The interval between eye movement bursts and twitches illustrates tonic REM sleep. [From Kryger *et al.* (1989) In: *Principles and Practice of Sleep Medicine*, W.B. Saunders Co., Philadephia, PA].

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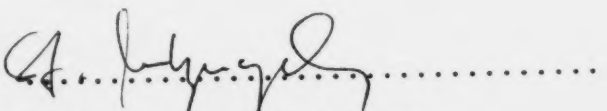

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ABSTRACT

Several authors have reported that there is an excess of the schizophrenia syndrome among narcoleptic patients. In addition, reports describing several schizophrenic patients with narcolepsy seem to show that a certain proportion of patients with schizophrenic symptoms have narcoleptic hallucinations (and their subsequent delusional elaboration) at the root of the psychiatric syndrome. The clinical presentation of these essentially narcoleptic patients is so dominated by psychotic symptoms that they are not easily distinguished from the general run of patients suffering from schizophrenic disorders and they have gone largely undiagnosed. The hypothesis that a substantial number of narcoleptic patients are missed diagnostically and medicated inappropriately is examined in this thesis. From 489 consecutive patients presenting to the Psychiatry Department of the University of Alberta, patients with symptomatically functional hallucinating psychoses were selected for this study. Of these, only 30 with inexplicable psychoses were retained. Furthermore, 2 adopted patients, 8 patients with a family history of severe psychoses, 6 patients with antecedent substance abuse, and 3 patients with brain damage were excluded. Of the 11 who remained, 5, that is about 20% of the psychotic patients with hallucinating schizophrenia-like psychosis, had clinical narcolepsy, and 3 of these (10%) had the diagnosis confirmed in the sleep laboratory.

These findings and the pitfalls that impeded their discovery, are discussed with the aim of working out a rational and economical approach to the diagnosis of narcolepsy in the setting of psychosis. All the approaches favoured require that they be implemented at an early stage of the diagnostic process.

ACKNOWLEDGEMENTS

I would like to recognize in particular Dr. P. Hays and Dr. G. Baker, without whom this project would not have been initiated or completed, for their knowledge and expertise as well as their support and encouragement that provided the impetus for this work. Special acknowledgement is due to Dr. A. Greenshaw for his advice, assistance and understanding.

To the Staff of the Sleep Disorders Laboratory, U. of A. Hospitals, in particular Dr. G. Man and Mrs. Rhoda Shreiner, I extend my appreciation for their support of the project activities.

I am grateful to to the physicians and nurses of the Department of Psychiatry, University of Alberta, for their assistance and support.

Finally, to Ms. Robyn Widdifield and Ms. Sally Omura, my thanks for patiently typing this thesis.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone
Catap.	Cataplexy
ChAT	Choline acetyltransferase
CNS	Central nervous system
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
H/H Halluc.	Hypnagogic/hypnopompic hallucination
HLA	Human lymphocyte antigen
5-HT	5-hydroxytryptamine; serotonin
MDP	Muramyl dipeptide
MHC	Major histocompatibility complex
MSLT	Multiple Sleep Latency Test
N	No
OSA	Obstructive sleep apnea
Polysom.	Polysomnography
REM	Rapid eye movement
REML	Rapid eye movement latency
SAD	Seasonal affective disorder
SL	Sleep latency
SOREM	Sleep-onset REM
Y	Yes

A. INTRODUCTION

This thesis concerns practical approaches to identifying examples of narcolepsy masquerading as "schizophrenia" in general psychiatric practice. First the terms Sleep, Narcolepsy and Schizophrenia will be explained.

A.1 Sleep and Its Architecture

Early mankind viewed sleep as a time when the soul left the body. This view of sleep persisted until the 19th century (Anch *et al.*, 1988). Most advances in sleep research, however, have occurred since 1940. For the study of sleep, the technological advance which contributed most to the field was the development of the electroencephalogram (EEG), allowing recording of the reflected electrical activity of the brain. The German psychiatrist, Hans Berger, was the first to record EEG in humans (Berger, 1929). Later, a group of scientists gave the first description of the various EEG patterns observed during sleep (Davis *et al.*, 1937). Aserinsky and Kleitman (1953) discovered the existence of rapid eye movement (REM) sleep, a separate state in which there is EEG activation, muscle atonia and bursts of eye movements. These workers also reported the association of dreaming and REM sleep.

In 1957, Dement and Kleitman found that periods of REM sleep alternate every 90 to 100 minutes with periods of non-rapid eye movement (NREM) sleep. NREM sleep is subdivided into four stages which are defined according to particular changes in EEG patterns discussed in more detail later in this thesis. They proposed the first scoring system in which NREM was divided into four stages and REM was a fifth stage of sleep. This scoring system, somewhat modified (Rechtschaffen and Kales, 1968), is still in use today. The findings of Dement and Kleitman (1957) marked the beginning of the modern era of sleep research.

What is sleep? According to a behavioural definition, "sleep is a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment" (Carskadon and Dement, 1989). Evidence from modern sleep research suggests that sleep is a very complex neurobiological and behavioural process to simultaneously promote energy regulation and automatically process information by the brain (Hobson, 1990). Why do we sleep? The sleep research findings which have evolved so far indicate that sleep is a complex amalgam of neurobiological and behavioural processes. The complex interactions of these processes promote energy regulation and information processing by

the brain at the same time. There are several theories of sleep function, and these include the restorative theory, energy conservation, adaptive theories, memory consolidation and an instinct theory.

The restorative theory indicates a role for NREM sleep in body tissue restoration and for REM sleep in brain tissue restoration (Moruzzi, 1972; Hartmann, 1973; Oswald, 1974; Adams and Oswald, 1977). A more specific restorative role for sleep was proposed by Moruzzi (1972), who stated that sleep is responsible for the restoration of neurons which are associated with conscious behaviour.

Others have perceived sleep as a period of energy conservation (Zepelin and Rechtschaffen, 1974). This theory simply says that immobility during sleep conserves energy.

Other researchers put forward the view that sleep enhances survival. This concept was the basis for adaptive theory of sleep function, in which it is suggested that sleep prohibits animals from interacting with the environment under maladaptive conditions, thereby promoting survival (Webb, 1975; Meddis, 1977).

Another theory proposed that sleep is an instinct like mating or migration (Moruzzi, 1972; McGinty *et al.*, 1974). This position does not reject other theories (e.g. adaptive and energy conservation theories) of sleep function and has not stimulated much research interest. It states that sleep is a species-specific behaviour which represents a response to stimuli that promote survival of the species.

Some researchers promoted the memory consolidation theory. It is known that information which we learn just before sleep will be remembered better (Jenkins and Dallenbach, 1924). Thus, perhaps REM sleep promotes storage of information. There is evidence that hormones and neurotransmitters modulate memory processes (McGaugh *et al.*, 1975). In their experiments on rats, they investigated the effects of catecholamines on learning by administering dopamine and norepinephrine into the cerebral ventricles. As a result, both catecholamines enhanced retention of newly learned responses, being consistent with the hypothesis that they may influence memory storage processes. In another experiment, these authors investigated the effects on memory storage with posttrial injections of several hormones (e.g. ACTH and

vasopressin). They found that retention was enhanced by injecting ACTH and also showed that several different hormones had similar effects on memory.

There have been new insights into sleep functions recently (Hobson, 1990). Temperature regulation, the immune system and cognitive functions are influenced by sleep and its stages as well. Sleep plays a role in energy conservation used by small mammals so they are able to cope with different levels of heat and light. For example, a daily temperature drop and hibernation both occur during NREM sleep favour the view that during sleep there is energy conservation used by mammals to cope with different levels of light and heat (Heller *et al.*, 1988). It is also known that infectious diseases cause sleepiness in humans (Hobson, 1990), but the mechanism is still not understood. It has, however, been shown that there are muropeptides in the cerebrospinal fluid which have powerful pyrogenic and immunostimulatory features (Krueger *et al.*, 1985b; Silverman and Karnovsky, 1989). Furthermore, interleukin-1, an endogenous peptide, has immunostimulatory and somnogenic properties. It is produced by glial cells and macrophages. Interleukin-1 and muramyl dipeptide (MDP) enhance phagocytic tumoricidal and bacteriocidal activity, as well as alter sleep in a similar manner (Krueger *et al.*,

1985a). Time spent in NREM, duration of individual episodes of sleep and amplitudes of slow waves are increased. However, REM sleep time is decreased by both compounds. Therefore, their contribution to the physiology of normal sleep remains still uncertain. Studies with humans also showed that attention, concentration, affect and motivation declined with sleep loss (Mikulincer *et al.*, 1989).

In spite of all these scientific attempts to find the purpose of our sleep, the question still remains open.

Within sleep, as described above, two distinct states have been defined: NREM and REM sleep (Table I). NREM sleep is subdivided into four stages (stages 1, 2, 3 and 4) which parallel a "depth of sleep" continuum. The arousal threshold is lowest in stage 1 and highest in stage 4 sleep. Stage 1 is characterized by mixed frequency of 2 to 7 Hz EEG rhythm and is a transitional phase between wakefulness and sleep. Stage 2 is characterized by the presence of sleep spindles and K complexes and EEG activity of 12 to 14 Hz. Stages 3 and 4 are defined by the presence of delta waves (2-4 Hz), 20% to 50% of them in stage 3 and greater than 50% in stage 4. REM sleep has an EEG pattern similar to that of stage 1 with the exception that "sawtooth" waves and

rapid conjugate eye movements are present. Normal sleep evolves each night in a somewhat predictable manner. It starts with Stage 1 lasting up to 10 minutes, which then gives way to stage 2 and, after about 45 minutes, to stages 3 and 4. There are 4-6 such sleep cycles per night for a young adult. The average duration of a sleep cycle is 90 minutes each and concludes with a period of REM. On average, adults sleep 7 to 8 hours per day. The presence of specific disorders of sleep leads to a reduction in efficiency and well-being, of course, but epidemiological studies have revealed that even in the absence of such specific disorders, both long and short sleepers have an increased mortality rate (Anch *et al.*, 1988).

TABLE I: NREM AND REM SLEEP CHARACTERISTICS IN MAN

Measurement	*NREM Sleep*	*REM Sleep*
Scalp EEG	Slow waves and spindles	Low voltage, mixed frequency
Hippocampal EEG	Variable	Rhythmic theta activity
Eye movements	None or few slow movements	Conjugate rapid movements
Chin EMG	Decreased from wakefulness	Almost absent
Body movements	A few gross movements	Twitches
Respiration	Regular, deep	Variable, shallow
Heart rate	Regular, slow	Variable, rapid
Blood pressure	Below waking level	Variable
Penile erection	Absent	Present
Mentation	Thought-like, repetitive	Dream-like, dramatic
Galvanic skin response	Frequent	Rare

[from Freemon (1972) *Sleep Research: A Critical Review*, Charles C. Thomas Publisher, Springfield, Ill.].

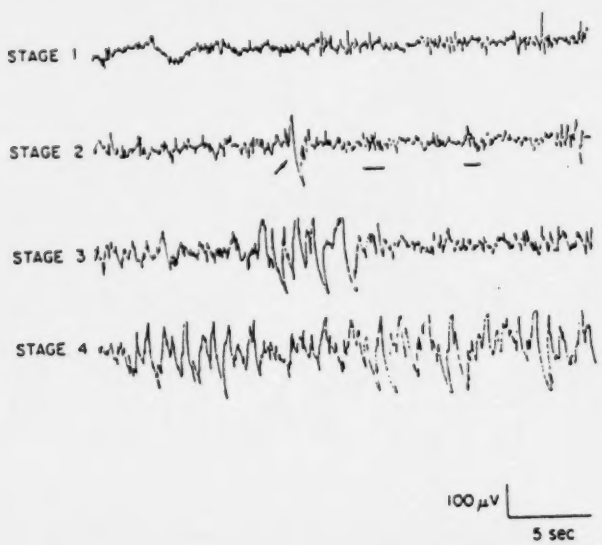

Figure I: The stages of NREM sleep. The four electroencephalographic (EEG) tracings depicted here are from a 19-year old female volunteer. Each tracing was recorded from a referential lead (C3/A2) recorded on a Grass Instruments Co. Model 7D polygraph with a paper speed of 10 mm/sec, time constant of 0.3 sec, and 1/2 amplitude high-frequency setting of 30 Hz. On the second tracing, the arrow indicates a K complex, and the underlining shows two sleep spindles. [From Kryger *et al.* (1989) In: *Principles and Practice of Sleep Medicine*, W.B. Saunders Co., Philadephia, PA].

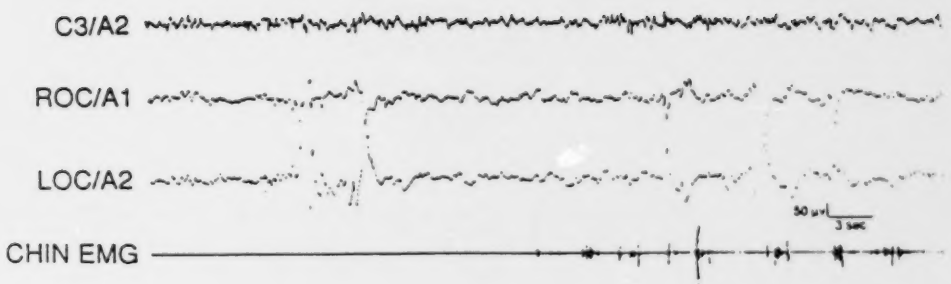

Figure II: REM sleep. Phasic events in human REM sleep are illustrated in this figure. On the left side is a burst of several rapid eye movements (out-of-phase deflections in ROC/A1 and LOC/A2). On the right side, there are additional rapid eye movements as well as twitches on the electromyographic (EMG) lead. The interval between eye movement bursts and twitches illustrates tonic REM sleep. [From Kryger *et al.* (1989) In: *Principles and Practice of Sleep Medicine*, W.B. Saunders Co., Philadephia, PA].

A.2 Sleep Disorders in Psychiatry

Most psychiatric illnesses can have associated sleep disturbances (Vogel *et al.*, 1989). To provide a better chance of more accurate diagnoses, the International Classification of Sleep Disorders was introduced by the American Sleep Disorders Association in association with the European Sleep Research Society, the Japanese Society of Sleep Research and the Latin-American Sleep Society. Classification outlines are as follows:

1. Dysomnias
   - A. Intrinsic Sleep Disorders
   - B. Extrinsic Sleep Disorders
   - C. Circadian Rhythm Sleep Disorders

2. Parasomnias
   - A. Arousal Disorders
   - B. Sleep-Wake Transition Disorders
   - C. Parasomnias Usually Associated With REM Sleep
   - D. Other Parasomnias

3. Medical/Psychiatric Sleep Disorders
   - A. Associated With Mental Disorders
   - B. Associated With Neurological Disorders
   - C. Associated With Other Disorders

4. Proposed Sleep Disorders

   A. Short Sleeper

   B. Long Sleeper

   C. Subwakefulness Syndrome

   D. Fragmentary Myoclonus

   E. Sleep Hyperhydrosis

   F. Menstrual-Associated Sleep Disorder

   G. Pregnancy-Associated Sleep Disorder

   H. Terrifying Hypnagogic Hallucinations

   I. Sleep-Related Neurogenic Tachypnea

   J. Sleep-Related Laryngospasm

   K. Sleep-Choking Syndrome

Sleep disorders associated with mental disorders include:

1. Psychoses
2. Mood Disorders
3. Anxiety Disorders
4. Panic Disorder
5. Alcoholism

The prominent disturbance is most often in the form of insomnia. However, occasionally patients will attribute their problems to excessive sleepiness, nightmares or parasomnia-type behaviours. It has been shown that 35-50% of chronic insomnia may be causally

related to psychiatric illness and about 75% of insomniacs may suffer from some degree of depression (Reite, 1990).

Sleep complaints are common in affective disorders, dysthymic disorder, hypomania and cyclothymia, schizophrenia, personality disorders, anxiety-related disorders, alcoholism and drug abuse. Insomnia or excessive sleepiness are common features of psychoses. Acute schizophrenic decompensation is often associated with increase in frequency of nightmares and severe difficulty in initiating sleep (Reite, 1990). The following polysomnographic characteristics of such patients might be seen: shortened REM latency, increase in REM density, increased sleep latency, decreased total sleep time and slow wave sleep (The International Classification of Sleep Disorders, 1990). Mood disorders have associated changes of sleep which are mainly made up of two patterns of insomnia: in depression, difficulty in falling asleep and early morning awakening; in mania, sleep-onset insomnia and short sleep duration. In major depression, the most characteristic feature of insomnia is the repeated awakenings with the cardinal complaint of waking up too early. Most patients complain of nocturnal restlessness and tired feelings, whereas in bipolar depression they mostly complain of excessive sleepiness

or, in milder cases, napping (Reynolds, 1989). Polysomnographic changes in major depression show a decreased continuity of sleep, reduced delta sleep and increased REM sleep with a characteristic decrease in nocturnal REM latency.

In bipolar disorder, sleep may exhibit REM changes similar to those seen in depression. The prominent feature in anxiety disorders is frequent awakening with or without anxious dreams. However, there is often coexistence of anxiety and depression (review: Nutt and Glue, 1991) which presents problems in differential diagnosis (Reite *et al.*, 1990). In polysomnography there are nonspecific findings of increased sleep latency, decreased sleep efficiency (total sleep time/total time in bed) and decreased slow wave sleep. Another interesting illness associated with excessive daytime sleepiness is seasonal affective disorder (SAD). It may be related to a circadian rhythm disturbance precipitated by the changes in the length of the day (Reite *et al.*, 1990). Finally, alcoholic patients often complain about sleep disruptions. Acute alcohol use produces increased sleepiness 30 minutes after consumption, and alcohol consumed before bed reduces wakefulness for the first 3-4 hours of sleep, but increases wakefulness for the last 2-3 hours of sleep. Alcohol use before sleep onset

causes increased incidence of sleep terrors, sleep walking, bed wetting and even precipitation of snoring and sleep apnea. Chronic excessive use of alcohol may be initially associated with sleep improvement but after several days of alcohol consumption sleep becomes fragmented, with periods of deep sleep interrupted by arousals or periods of restlessness (Gillin, 1989; Reite *et al.*, 1990). In psychiatric disorders, the sleep complaints usually parallel the state of the illness, improving when psychiatric symptoms improve. Also, it is not always clear whether the psychiatric illness precipitates the sleep disorder or vice versa. These concerns stress the significance of a thorough psychiatric evaluation as an important part of sleep history taking.

A.3 Narcolepsy

The word narcolepsy was coined by Gelineau (1880), who described irresistible episodes of sleep sometimes accompanied by falls. Daniels (1934) called major narcoleptic symptoms the clinical "tetrad": cataplexy, sleep paralysis, hypnopompic/hypnagogic hallucinations, and sleep attacks. Cataplexy is characterized by sudden loss of bilateral muscle tone provoked by strong emotion. During this phenomenon, consciousness remains clear, memory is not impaired and respiration is intact. The

duration of cataplexy is usually a few seconds to several minutes. Sleep paralysis is defined as a brief inability to move or to speak during the transition between sleep and wakefulness. Hypnagogic hallucinations occur mainly in the auditory modality but can be visual or tactile as well. They can be defined as perceptual experiences of the presence of someone or something and they include visual, tactile, auditory and olfactory phenomena with retention of some awareness of the environment. Hypnagogic hallucinations are experienced during the transition from wakefulness to sleep or, less commonly, during recovery from sleep (hypnopompic hallucinations).

A brief account of the development of our knowledge of sleep was presented in the previous section. The description of the syndrome has evolved in association with our increasing knowledge of sleep architecture. In 1975, during the first International Symposium on Narcolepsy, held in France, the syndrome was freshly defined in a more sophisticated but essentially similar way to that of Daniels, now making reference to REM sleep as follows (quoted in Kryger *et al.*, 1989):

> "The word narcolepsy refers to a syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness and often disturbed

nocturnal sleep and pathological manifestations of REM sleep. The REM sleep abnormalities include sleep onset, REM periods and the dissociated REM sleep inhibitory processes cataplexy and sleep paralysis. Excessive daytime sleepiness, cataplexy, and less often sleep paralysis and hypnagogic hallucinations are the major symptoms of the disease".

A more recent description of the syndrome was defined in the International Classification of Sleep Disorders in 1990:

"Narcolepsy is a disorder of unknown etiology which is characterized by excessive sleepiness that typically is associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations".

All definitions continue to include the four major symptoms (the tetrad). Etiologically, narcolepsy can be classified into two types: idiopathic and symptomatic, although this classification remains controversial (Williams *et al.*, 1988). Another way of classifying the syndrome is according to the occurrence of the components of the narcoleptic tetrad, the monosymptomatic form having only one symptom and the polysymptomatic form

having more than one symptom. By far the most frequent form of narcolepsy, however, is the polysymptomatic, making up 65% to 75% of all cases. The prevalence of this disorder has been reported to lie between 0.1% and 0.01% in Europe and USA (Aldrich, 1990). The usual time of onset is between 15 and 35 years of age and men and women are affected equally. Excessive daytime sleepiness is the classical hallmark of narcolepsy and is characterized by repeated episodes of sleep lasting usually 10 to 20 minutes followed by refreshed awakening. The only pathognonomic feature of the syndrome is a history of cataplexy which is the sudden partial or complete loss of muscle tone provoked by strong emotion such as laughter, anger or surprise. During such an attack, consciousness, memory and respiration remain intact and recovery is immediate and complete. In the course of onset of narcolepsy, sleepiness usually begins months before the development of cataplexy; 6% to 10% of patients have cataplexy initially, and 10% to 15% develop it within 10 years after the onset of sleepiness (Aldrich, 1990). Sleep paralysis and hypnagogic hallucinations occur in about 60% of narcoleptics (Aldrich, 1990) and they are the consequence of sleep-onset REM periods (REM appearing within 20 minutes after sleep onset).

A.3.1 Heritability of Narcolepsy

It is known that narcolepsy occurs often in families. However, the genetic basis was unknown until a recent discovery of a strong linkage of the illness to human lymphocyte antigen [HLA] (Aldrich, 1991). This linkage of narcolepsy with the HLA haplotype DR2/DQW1 localizes the gene on the short arm of human chromosome 6 within the major histocompatability complex [MHC] (Cheney, 1992). It has also been recognized that approximately 98% of Caucasians with narcolepsy carry this type of HLA. There is, however, a 20-35% incidence of the HLA-DR2 and HLA-DQW1 antigens in the normal population. Both HLA-DR2 and HLA-DQW1 have been recognized as having 100% association with DRW15 and DQW6 subtypes, respectively, in narcoleptic patients. It has also been shown that of the HLA-D antigens, narcolepsy has a strong association with DW2 (Aldrich, 1991). The HLA-DR2 incidence varies in different populations, e.g. > 99% in Japanese narcoleptics and 91-98% in Caucasians. North American black narcoleptics have an incidence of DQW1 in over 90% but the incidence of DR2 is only 65-70%. It has been noticed that there is the existence of familial HLA-DR2 negative narcolepsy which suggests that there may in fact be a second narcolepsy susceptibility gene.

Furthermore, it could be possible that the gene linked to HLA-DR2 is not necessary in all cases for the expression of the "narcolepsy gene" which could be located anywhere in the genome (Aldrich, 1991).

Also, the relative frequencies of homozygotes and heterozygotes for DR2 (DRW15), DQW1 (DQW6) and DW2 support a dominant mode of inheritance. It can be concluded that while genetic susceptibility is an important determinant, there is evidence from monozygotic twin studies suggesting strongly that environmental influences are also quite significant (Aldrich, 1991).

There is also a possibility that an immunologic event precipitates narcolepsy by destruction of a neuronal cell surface protein with permanent down-regulation of activity at noradrenergic α_1 synapses (Aldrich, 1991). This particular possibility can be assumed by the association of HLA-DR2 and DQW1 with some autoimmune diseases and reduced binding of muramyl peptides to β lymphocytes in individuals with the DR2/DQW1 phenotype.

Therefore, the future research of the genetic basis of narcolepsy is still of crucial importance.

A.3.2 Neurochemical Aspects of Narcolepsy

Neurochemical research has also suggested disturbed monoaminergic and cholinergic function in narcolepsy, with a deficit of noradrenaline in specific brain regions proposed to account for pathophysiology of the syndrome (Aldrich, 1991). It has also been demonstrated that the pons is the most critical site for the generation of sleep; specifically, the regions of the pontine tegmentum are essential for permitting REM sleep to occur (Aldrich, 1991). As far as the neurochemistry of REM sleep is concerned, it is clear that acetylcholine plays an essential role. It has been shown that administration of cholinergic agonists into the pontine tegmentus facilitates REM sleep (Baghdoyan, 1989). The same authors state that there are a number of neurons with immunoreactivity for choline acetyltransferase (ChAT) in the locus coeruleus and many pontine REM-on cells seems to be cholinergic.

Within the brainstem there are REM-on cells and REM-off cells. It appears that many REM-on cells are cholinergic or cholinoceptive or both. Most of the REM-off cells of the brainstem are monoaminergic and they contain 5-hydroxytryptamine (5-HT, serotonin) or noradrenaline (Aldrich, 1991). Pharmacological treatment of narcolepsy triggers monoaminergic activity

which agrees with the concept that monoamine inhibition of REM sleep in narcolepsy is inadequate. Tricyclic antidepressants, on the other hand, used mainly for cataplexy, inhibit reuptake of monoamines (Hytell, 1982). They suppress cataplexy, suggesting that the cholinergic pathways can be inhibited by enhanced serotoninergic or noradrenergic activity. Studies of human narcoleptic brains revealed that there is increased dopamine D_2 receptor density in the caudate and putamen (Aldrich, 1991).

It is still unclear to what extent neurochemical findings such as changes of the receptors are related to previous stimulant medication.

A.3.3 Structural Theories of the Syndrome

There are some theories which suggested a diencephalic or midbrain lesion being responsible for the syndrome (Lishman, 1987). Occasionally examples have been reported with tumors, inflammations or degenerative processes involving the hypothalamus, head injuries, and in associaton with multiple sclerosis, cerebral arteriosclerosis or general paresis (Sours, 1963). However, most of the cases with cerebral pathology are more properly regarded as hypersomnias rather than narcolepsy.

A.3.4 Medical Treatment of Narcolepsy

The medical treatment of narcolepsy depends on the long-term use of central nervous system (CNS) stimulants (analeptics) such as caffeine and amphetamines, together with various auxiliary medications (Anch *et al.*, 1988). The drug therapy is used in a setting of regular sleep schedules, judicious naps and cups of coffee or tea. Three principal stimulant preparations are usually prescribed, namely methylphenidate (10 to 60 mg), dextroamphetamine (5 to 50 mg) or pemoline [37.5 to 75 mg] (Aldrich, 1990). They can lead to euphoria and anorectic and sympathomimetic side-effects (Guilleminant, 1989). For patients with cataplexy or sleep paralysis which remains a problem, tricyclic antidepressants, such as the non-sedating drug protriptyline, are used. These work by inhibiting the reuptake of noradrenaline and 5-HT (Aldrich, 1990). Strong inhibitors of 5-HT reuptake, e.g. clomipramine and fluoxetine, or of noradrenaline reuptake such as desipramine, may have the same effect as protriptyline with fewer anticholinergic side effects (Guilleminault, 1989; Aldrich, 1990).

As the drug regimen is established and made more precise, the naps can be adjusted. Generally, they should not exceed 15 to 20 minutes. They may be so effective as reducers of drowsiness that the dosage of pharmacological stimulants can be lessened. Patients with narcolepsy find it difficult to regulate their bed time and waking time, and at the outset of treatment their efficiency is impaired by their sleep debt. Counselling to allow for behavioural change is therefore usually necessary for optimal results (Aldrich, 1990).

A.4 Schizophrenia

Schizophrenia describes a range of mental disorders and has been recognized in all cultures throughout much of recorded time (Storey, 1986). It is a very common and probably one of the most devastating psychiatric illnesses, affecting about 1% of the population between 15 and 45 years of life (Wyatt *et al.*, 1988). The concept of schizophrenia will probably be best understood historically.

Kraepelin (1971) formulated the concept of schizophrenia (then called dementia praecox) as a unitary disease. Before him, most of the mentally ill were grouped together as "insane". Later Bleuler renamed

dementia praecox, suggesting the name "schizophrenia" which emphasized the cognitive impairment ("splitting" of the psychic processes).

Kurt Schneider, the German psychiatrist, introduced first rank symptoms. These clear-cut symptoms were useful in diagnosing schizophrenia (Andreasen, 1991). In these symptoms, Schneider included voices commenting on a person's actions, arguing with each other about a patient or repeating the patient's thoughts. Delusions included thought broadcasting, thought withdrawal, and thought insertion.

At present, schizophrenia is universally defined in syndromal terms because, since the cause is not known, no other way is feasible (Hays, 1984). It is also useful to describe schizophrenic symptoms as either positive or negative with the frequency presented in Table II. Positive symptoms include hallucinations, delusions, positive formal thought disorder, and bizarre behaviour. Negative symptoms include affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention impairment (Andreasen, 1987).

The most commonly used diagnostic criteria for schizophrenia are those elaborated by the American Psychiatric Association in the *Diagnostic and Statistical*

Manual of Mental Disorders, 3rd Edition - Revised, known in abbreviation as DSM-III-R (American Psychiatric Association, 1987). The diagnostic criteria for schizophrenia are set out in Table III.

Despite this formal commitment to syndromal diagnosis, the original idea that schizophrenia is the consequence of a single morbid process still colours psychiatric thinking and, after it has been defined as a syndrome, the state is commonly, though erroneously, thought of and spoken of as a disease (Dalen and Hays, 1990).

A.5 Connections Between Narcolepsy and Schizophrenia

Having defined the terms narcolepsy and schizophrenia, we may now consider the relationships of these conditions.

Several authors have reported a high incidence of schizophrenia among narcoleptics (Smith, 1958; Sours, 1963; Roy, 1976; Wilcox, 1985). Some of these psychoses were due to the amphetamines used to manage the illness, and a case of amphetamine psychosis in a narcoleptic was described as early as 1938 (Young and Scoville, 1938). But any assumption that all or most of the psychoses seen in narcoleptics were amphetamine-related did not stand up

to detailed scrutiny: crucially, many patients had become psychotic before stimulants were used (personal communication with Dr. P. Hays).

TABLE II:

Frequency of symptoms in 111 schizophrenic patients

Symptom	%	Symptom	%
NEGATIVE SYMPTOMS		POSITIVE SYMPTOMS	
• Affective flattening		• Hallucinations	
Unchanging facial expression	96	Auditory	75
Decreased spontaneous movements	66	Voices commenting	58
Paucity of expressive gestures	81	Voices conversing	57
Poor eye contact	71	Somatic-tactile	20
Affective nonresponsivity	64	Olfactory	6
Inappropriate affect	63	Visual	49
Lack of vocal inflections	73		
		• Delusions	
• Alogia		Persecutory	81
Poverty of speech	53	Jealous	4
Poverty of content of speech	51	Guilt, sin	26
Blocking	23	Grandiose	39
Increased response latency	31	Religious	31
		Somatic	28
• Avolition-apathy		Delusions of reference	49
Impaired grooming and hygiene	87	Delusions of being controlled	46
Lack of persistence at work or school	95	Delusions of mind reading	48
Physical anergia	82	Thought broadcasting	23
		Thought insertion	31
• Anhedonia-asociality		Thought withdrawal	27
Few recreational interests/activities	95		
Little sexual interest/activity	69	• Bizarre behavior	
Impaired intimacy/closeness	84	Clothing, appearance	20
Few relationships with friends/peers	96	Social, sexual behavior	33
		Aggressive-agitated	27
• Attention		Repetitive-stereotyped	28
Social inattentiveness	78		
Inattentiveness during testing	64	• Positive formal thought disorder	
		Derailment	45
		Tangentiality	50
		Incoherence	23
		Illogicality	23
		Circumstantiality	35
		Pressure of speech	24
		Distractible speech	23
		Clanging	3

Source. Adapted from Andreasen NC: The diagnosis of schizophrenia. Schizophr Bull 13:9–22, 1987

[from Andreasen and Black (1991) *Introductory Textbook of Psychiatry*, American Psychiatric Press, Washington, D.C.].

TABLE III: DSM-III-R CRITERIA FOR SCHIZOPHRENIA

(A) Presence of characteristic psychotic symptoms in the active phase: either (1), (2) or (3) for at least 1 week (unless symptoms are successfully treated):

(1) Two of the following:

a. delusions

b. prominent hallucinations (throughout the day for several days or several times a week for several weeks, each hallucinatory experience not being limited to a few brief moments)

c. incoherence or marked loosening of associations

d. catatonic behaviour

e. flat or grossly inappropriate affect

(2) Bizarre delusions (i.e. involving a phenomenon that the person's culture would regard as totally implausible, e.g. thought broadcasting, being controlled by a dead person).

(3) Prominent hallucinations [as defined in (1b) above] of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person's behaviour or thoughts of two or more voice conversing with each other.

(B) During the course of the disturbance, functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved before onset of the disturbance (or, when the onset is in childhood or adolescence, failure to achieve expected level of social development).

(C) Schizoaffective disorder and mood disorder with psychotic features have been ruled out; i.e., if a major depressive or manic syndrome has ever been present during an active phase of the disturbance, the total duration of all episodes of a mood syndrome has been brief relative to the total duration of the active and residual phases of the disturbance.

(D) Continuous signs of the disturbance for at least 6 months. The 6-month period must include an active phase (of at least 1 week, or less if symptoms have been successfully treated) during which there were

psychotic symptoms characteristic of schizophrenia [symptoms in (A) above], with or without a prodromal or residual phase, as defined below.

Prodromal phase: A clear deterioration in functioning before the active phase of the disturbance that is not due to a disturbance in mood or to a psychoactive substance use disorder and that involves at least two of the symptoms listed below.

Residual phase: Following the active phase of the disturbance, persistence of at least two of the symptoms noted below, those not being due to a disturbance in mood or to a psychoactive substance use disorder.

Prodromal or residual symptoms:

1. Marked social isolation or withdrawal.
2. Marked impairment in role functioning as wage earner, student or homemaker.
3. Marked peculiar behaviour (e.g., collecting garbage, talking to self in public, hoarding food).
4. Marked impairment in personal hygiene and grooming.
5. Blunted or inappropriate affect.
6. Digressive, vague, overelaborate, or circumstantial speech, or poverty of speech, or poverty of content of speech.
7. Odd beliefs or magical thinking, influencing behaviour and inconsistent with cultural norms, e.g., superstitiousness, belief in clairvoyance, telepathy, "sixth sense", "others can feel my feelings", overvalued ideas, ideas of reference.
8. Unusual perceptual experiences, e.g., recurrent illusions, sensing the presence of a force or person not actually present.
9. Marked lack of initiative, interests, or energy.

Examples: Six months of prodromal symptoms with 1 week of symptoms from (A); no prodromal symptoms with 6 months of symptoms from (A); no prodromal symptoms with 1 week of symptoms from (A) and 6 months of residual symptoms.

(E) It cannot be established that an organic factor initiated and maintained the disturbance.

(F) If there is a history of autistic disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present.

Classification of Course: The course of the disturbance is coded in the fifth digit:

1 - Subchronic. The time from the beginning of the disturbance, when the person first began to show signs of the disturbance (including prodromal, active, and residual phase) more or less continuously, is less than 2 years, but at least 6 months.

2 - Chronic. Same as above, but more than 2 years.

3 - Subchronic with acute exacerbation. Reemergence of prominent psychotic symptoms in a person with a subchronic course who has been in the residual phase of the disturbance.

4 - Chronic with acute exacerbation. Reemergence of prominent psychotic symptoms in a person with a chronic course who has been in the residual phase of the disturbance.

5 - In remission. When a person with a history of schizophrenia is free of all signs of the disturbance (whether or not on medication), "in remission" should be coded. Differentiating schizophrenia in remission from no mental disorder requires consideration of overall level of functioning, length of time since the last episode of disturbance, total duration of the disturbance, and whether prophylactic treatment is being given.

0 - Unspecified.

[from Andreasen and Black (1991) *Introductory Textbook of Psychiatry*, American Psychiatric Press, Washington, D.C.

Original source: American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*, American Psychiatric Association, Washington, D.C.].

Real or fancied parallels between dreaming and madness are commonplace, and it was natural that sleep researchers should propose that psychotic phenomena might be waking dreams. Gillin and Wyatt (1975) reviewed sleep laboratory findings on schizophrenic patients and found no evidence of REM intrusion, that is, of daytime dreamlike phenomena in schizophrenics. Reviewing phenomenology of hallucinations and dreams, these authors concluded that "it would be surprising if dreams and hallucinations were identical". However, the similarity between dreams and hallucinations may suggest that the mechanisms producing these processes could be related. This area remained quiescent until the publication of a case report by Douglass and Hays (1987). These authors described a patient whose narcoleptic symptoms, notably her hallucinations and sleep paralysis, so resembled those described by patients with schizophrenic psychosis that she had been diagnosed and treated as schizophrenic. Subsequently these authors, now associated with other collaborators, looked for fresh examples of narcolepsy masquerading as "schizophrenia" and published an account of their findings (Douglass *et al.*, 1991). They stated that:

> "Narcolepsy in which the hallucinatory component is unusually prominent may lead to

> the development of an illness indistinguishable from the schizophrenic syndrome. Psychotic symptoms dominate the symptomatology, so that the primary illness is obscured ... as many as 7% of a series of schizophrenic patients are likely to have narcolepsy as the basic process responsible for the psychotic symptoms."

Summary of Introduction

From the evidence reviewed above, it is apparent that there are some cases called schizophrenia which could more properly be called narcolepsy. In any diagnostic scheme a specific diagnosis such as narcolepsy (with a distinct syndrome, a genetic basis, a familial incidence and treatment of predictable effect) is conceptually superior to, and must take precedence over, a "diagnosis" such as schizophrenia (syndromally ascertained and without any basis in systematic observation). The question of how to diagnose narcolepsy in the presence of a schizophrenic syndrome arises naturally out of these considerations.

Asking questions designed to elicit the tetrad of narcolepsy (sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations) is not currently part of the approach when assessing patients with psychosis. But

clearly, if a sizeable proportion of those displaying the schizophrenic syndrome are really narcoleptic, some practical way of screening for them should be worked out as soon as possible, and incorporated into the existing clinical framework.

No simple screening method is presently available. Any method currently in use is expensive, time-consuming or both. It is necessary at the outset to reduce as far as possible the numbers of patients upon whom to focus attention. We are looking for narcolepsy which explains the psychosis. If the psychosis under review already has an explanation then we would be justified in this preliminary inquiry in discarding the patient. Therefore if we would find drugs or organic causes lying at the basis of a psychotic illness, we would exclude such patients from our attention. No functional psychosis has a complete explanation, but even a partial explanation would suffice as an exclusion criterion in this research setting.

A.6 Objectives of the Study

The aims of the study were (i) to discover the incidence of schizophreniform illnesses which were the product of underlying narcolepsy and (ii) to determine a practical method of identifying such patients.

(i) Incidence:

The estimate offered by Douglass *et al.* (1991) was that about 7% of hallucinated schizophrenic patients were essentially narcoleptic, with all their psychotic symptoms arising in a comprehensible manner from the basic narcoleptic tetrad. It is important that this proportion be ascertained by the study of further series such as that in the present inquiry. Obviously, if the proportion approaches 10% then patients with hallucinated psychoses should be considered with the diagnosis of narcolepsy at the forefront of the clinician's mind. Other processes (such as temporal lobe epilepsy) [Slater *et al.*, 1963] causing psychoses which fulfill the criteria for schizophrenic disorder exist and are often put forward in a differential diagnosis, but narcolepsy contributes perhaps more, approaching one-fifteenth (7%) of the morbidity of hallucinated schizophrenics [Douglass *et al.*, 1991]. On the other hand, if the proportion of psychoses caused by narcolepsy is nearer 1-2%, then systematic screening of all hallucinated psychotics to ascertain the presence or absence of narcolepsy will be less productive of treatable subjects and no matter how gratifying to the occasional individual who is identified and treated, such screening will be less justifiable economically. Douglass and Hays (personal communication)

have continued to frequently identify narcoleptic patients among their symptomatically schizophrenic patients.

(ii) Practical method of identifying narcoleptic patients:

Narcolepsy is easy to diagnose if the tetrad is present, less so if fewer symptoms exist. I aimed to discover the most economical and simple way of diagnosing narcolepsy in this population.

A.6.1 History

Some symptoms or complaints made by psychotic narcoleptics are easy to relate to the classical tetrad. Daytime sleepiness and refreshing naps are typical. Hallucinations occur in both narcoleptic and non-narcoleptic psychoses but in narcolepsy they are worse at night or if the patient is tired or bored (Anch *et al.*, 1988). Sleep paralysis will often be described obliquely, for example by saying that intruders hold the patient down. Delusions or accusations about sexual abuse may have their origin in nocturnal hallucinations or daytime REM states. The description of cataplexy may be phrased so that it elicits the concept of passivity in the mind of the listener. Gaps in awareness, due to lapses into sleep,

may reinforce delusions about intruders, because objects are moved or go missing. As Douglass *et al.* (1991) noted, psychotic narcoleptic patients are often obsessional in their premorbid personalities. Patients with narcoleptic psychoses may have a family history of sleepiness or obsessionality but will seldom have a family history of psychosis. Usually their illnesses do not follow substance abuse (Douglass *et al.*, 1991).

A.6.2 Mental Status Examination

Patients describe their experiences, of magic travel, of sexual assault or of companions, with great sincerity and in detail. They are not thought-disordered, except that they may skate over incongruities in their accounts, and otherwise their stories are consistent and systematized and may show some evidence of obsessionality (Douglass *et al.*, 1991). Narcoleptic patients may have scars from self-mutilation, undertaken when made desperate by hallucinatory voices.

A.6.3 Investigations

The EEG is essentially normal in narcolepsy, except that the patient may soon become drowsy (Lishman, 1987).

A.6.4 Sleep Laboratory Studies

Since these tests were used in the investigation reported in this thesis, a full account of how they are used is offered here.

A.6.4.1 Polysomnography

This is a procedure during which one can record different physiological variables during sleep by means of the electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (chin EMG).

Typically, to study physiological parameters we monitor bioelectric potentials from various parts of the body (Anch *et al.*, 1988). The signals measured are small in voltage level (one microvolt to one millivolt), so they are amplified in order that they may be recorded and interpreted. Some of them are slow (0.001 to 0.01 Hz) and some of them are very fast (1000 to 2000 Hz) in frequency. The most relevant range of the faster signals is 0.3 to 20 Hz, so that polysomnography requires not only proper amplification but also filtering out the extreme frequencies. Then the modified signals are recorded on chart paper, to be evaluated after completion of the test. In addition, recordings involve measurement of oxygen saturation, nasal and oral airflow, thoracic and abdominal

respiratory movements, leg muscle activity and electrocardiogram (Reite *et al.*, 1990). Thus a fairly comprehensive account of the patient's physiology during a night's repose is obtained.

The sleep latency (that is the time it takes to fall asleep) for a normal subject is 10 to 20 minutes. Narcoleptics fall asleep more quickly, with a sleep latency of 5 minutes or less. In normal subjects, the first REM period takes place after 60 to 90 minutes. Narcoleptics may enter REM sooner than this and in a classical instance will show sleep-onset REM (SOREM), that is REM which comes on in less than 20 minutes from the start of sleep (Carskadon *et al.*, 1986; Kales *et al.*, 1987).

A.6.4.2 Multiple Sleep Latency Test (MSLT)

MSLT documents impairment of daytime alertness. Not only does it measure daytime sleepiness, but it discloses early SOREM. This test is repeated at 2-hour intervals, and includes five 20-minute naps measuring the patient's tendency to fall asleep when in a relaxed state in bed. The mean latency to sleep helps in differentiating patients with normal alertness from those with excessive daytime sleepiness. The type of sleep occurring during naps is diagnostically useful as

two or more SOREM periods during the test are diagnostic for narcolepsy. Sleep should have been recorded overnight prior to the MSLT as disturbances in the quality or quantity of nocturnal sleep will influence the results obtained on the MSLT (Williams *et al.*, 1988).

A normal subject may fall asleep in some or all naps but will do so with a mean sleep latency of greater than 20 minutes and with no REM. Narcoleptics fall asleep in almost all naps, do so more rapidly with a mean sleep latency of less than 10 minutes and manifest REM in two or more naps (The International Classification of Sleep Disorders, 1990).

A.6.4.3 Human Leukocyte Antigen (HLA) Typing

It has been established that human narcolepsy is a genetic disease (Aldrich, 1991). There is a strong linkage of narcolepsy to Class II HLA haplotype DR2/DQW1, localizing the narcolepsy gene within the major histocompatibility complex (MHC) on the short arm of human chromosome 6. International studies have demonstrated that the incidence of HLA-DR2/DQW1 antigens exceed 90% in narcoleptics as compared to a 20% to 35% incidence in the rest of the population. However, it has been observed that there are some cases

of narcolepsy which are not associated with HLA-DR2. This observation supports that initial reports of an almost 100% incidence of HLA-DR2 with the syndrome, as the antigen uniquely responsible for "narcoleptic susceptibility" could be incorrect. In the absence of brain damage, this would suggest a second type narcolepsy susceptibility gene and also that the gene linked to HLA-DR2 is not necessary in all cases for the expression of the narcolepsy gene, which in fact may be located anywhere in the human genome (Aldrich, 1991).

It has also been claimed that there are two subtypes of HLA-DR2 and HLA-DQW1 which show a 100% association with narcolepsy. These are the DRW15 subtype of HLA-DR2 and DQW6 subtype of HLA-DQW1 (Aldrich, 1991).

Although a familial tendency of narcolepsy has been known since Gelineau's report in 1880, most cases are sporadic (Cheney, 1992). The number of multigenerational families is small for linkage analysis. The possibility of an immunologic basis for narcolepsy has been suggested on the basis of the association of DR2/DQW1 phenotype with some autoimmune diseases and the reduced binding of mucamyl peptides to β-lymphocytes in these individuals (Aldrich, 1991). It is possible that immune-mediated destruction of a

neuronal cell surface protein with down regulation of noradrenergic α_1-receptors may be the precipitating cause for clinical narcolepsy. Neurochemical postmortem studies have shown low concentrations of free dopamine and of its metabolite homovanillic acid in the cerebrospinal fluid (CSF) of narcoleptics and also evidence of increased dopamine D2-receptor density in the basal ganglia, which findings are consistent with impaired dopamine release (Aldrich, 1991).

A.6.4.4 Feasible Approaches in an Exploratory Study

As already noted, it is necessary to reduce the numbers of patients upon whom we will concentrate our limited resources. In some instances a psychotic patient will have narcolepsy so classical and severe that the diagnosis would have been made before any connection had been described between narcolepsy and schizophreniform disorder (Douglass *et al.*, 1991). One way of reducing the number of patients to study would be to ask all patients, whether psychotic or not, about disorders of sleep. This is the practice followed by Hays (personal communication) and it provides diagnostic benefit for little expenditure of time, but it is not one which is as yet generally followed or taught. Sifting syndromes by systematic history-taking will isolate a group of patients whose symptoms make it

likely that a high proportion have narcolepsy. But the majority of patients seen in a psychiatric practice, taken as a whole, will not have narcolepsy, and the procedure will not be welcomed by general psychiatrists who already have to cut corners in their diagnostic interviews to maintain a reasonable flow of patients.

About 20% of the general population has the HLA-DR2 and/or HLA-DQW1 association when tissue-typed (Aldrich, 1991). If we assume that this distribution of HLA-DR2 and DQW1 holds for patients with the syndrome of schizophrenia, then about 80% of the schizophrenic patients will not have that association. Since almost all narcoleptics do have the association, there will be no purpose in looking for narcoleptics among the schizophrenics who do not have the HLA-DR2 and/or HLA-DQW1 association. This means that if we HLA-typed all our schizophrenic patients, we could reduce the numbers among whom we had to seek the tetrad of narcolepsy by 80%. Because HLA typing is expensive, this possible preliminary screening would be difficult to justify unless the institution concerned was unusually well funded.

If all schizophrenic patients, meaning all those who satisfy DSM-III-R criteria for schizophrenic disorder, were given a full sleep laboratory

assessment, then a proportion (estimated at not less than 7% by Douglass *et al.*, 1991) would be found to have narcolepsy. But nocturnal polysomnography and MSLT are even more expensive than HLA typing. When interpreting sleep records in the Sleep Laboratory, the diagnosis of narcolepsy is made most commonly on the basis of MSLT abnormalities rather than nocturnal polysomnographic findings. MSLT is naturally cheaper than the full test and offers an alternative approach. But all sleep laboratory investigations require the patient to be drug-free, achieving which may be dangerous or (for example, because it requires admission to a hospital ward) expensive. This regimen is quite important because practically all psychiatric medications influence sleep and its architecture (Nicholson *et al.*, 1989).

Finally, numbers could be reduced to manageable proportions by excluding from further scrutiny those patients about the etiology of whose illnesses we feel little doubt. If we are looking for psychoses which can be explained by narcolepsy, we can put to one side those illnesses which do not call for further explanation. Although no published reports exist to support this proposition, Hays (personal communication) states that the advent of narcolepsy sometimes seems to

precipitate psychoses in those who are constitutionally predisposed and believes that affective illnesses are more common among narcoleptics than among the general population. If correct, this implies, of course, that narcolepsy and familial psychoses are not totally separate things, and thus that excluding patients with familial psychoses as if they were also non-narcoleptic is not a completely justifiable procedure.

A disproportionate number of patients with schizophreniform psychoses have abused drugs or alcohol, and correlational evidence also indicates that these unfortunate combinations play a causal role in the development of psychoses (Tennant and Groesbeck, 1972). By the same logic as used when considering excluding patients with family histories of psychoses, we could reduce numbers carefully by excluding patients with antecedent drug or alcohol abuse. Correspondingly, though, the caveat is that probably drug and alcohol abuse are more likely to happen in narcoleptics and/or that drug abuse can cause or worsen narcolepsy. However, even if substance abuse and narcolepsy are not totally separate things, they are not so regularly associated that discarding patients with antecedent substance abuse would sharply reduce the numbers of narcoleptics among those who remain.

Other insults to the CNS increase the chances of psychosis, and excluding patients with brain damage, though a small proportion may have "acquired narcolepsy", will also be a helpful manoeuvre (Lishman, 1987).

Reviewing the possible ways of screening for narcolepsy shows that many practical difficulties lay in our way. It is the existence of these difficulties, of course, which makes this study worthwhile. Therefore, if this investigation discovers methods which work and they are inexpensive at the same time, they will be of important general value.

B. METHODOLOGY

Approval by the Ethics committee (Faculty of Medicine, University of Alberta) and the Special Services and Research Committee (University of Alberta Hospitals) was obtained at the outset.

B.1 Subjects

B.1.1 Inclusion Criteria

The charts of all patients admitted to the Psychiatric Wards at the University of Alberta Hospitals were scrutinized to see if they described a hallucinating schizophreniform psychoses. Any new patients referred to Dr. P. Hays of the Department of Psychiatry were reviewed to see if they had been diagnosed in the past as schizophrenic and were hallucinating. Those selected by these means were reviewed further.

B.1.2 Exclusion Criteria

Any patient with a first-degree relative with a history of functional psychosis (schizophrenia or bipolar illness) was excluded, as was any adopted patient. Those with a history of substance abuse

immediately antecedent to the hallucinations and any patient with evidence of brain damage or an abnormal or asymmetric EEG were excluded.

B.2 Materials and Methods

Those of the remaining patients who gave informed consent were interviewed and their histories reviewed with them to see whether the narcoleptic tetrad was present. All the staffmen admitting patients to the Psychiatric Ward at the University of Alberta Hospitals had agreed in advance that their patients could be interviewed in this way and for this purpose. Naturally, however, the question of proceeding to a full sleep study was in each case a matter for further discussion. In most instances patients were receiving antipsychotic drugs of various kinds by the time they were interviewed by the investigator. This virtually ruled out an informative nocturnal polysomnographic study unless all of the patient's drugs were withdrawn for a full two weeks in advance of the test.

The aim in general was to proceed to a full sleep study if this was clinically indicated, with modification of this aim if practical or ethical objection to a full study interfered with the overall plan.

A full sleep study was conducted as follows: the patients reported to the Sleep Laboratory between 9:00 and 10:00 p.m. They were asked not have any meals or beverages after 6:00 p.m. before the study. They had also agreed not to take any medication for 14 days prior to the study. None of the subjects had any known physical disorder.

The patients slept in sound-shielded separate rooms that were maintained at steady temperature. The laboratory was equipped with television cameras and microphones to maintain one-way visual and two-way audio communication between the patient in the sleep room and the technician. A video cassette recorder could be used as well to document the person's movements during sleep, but in our study video recordings were not used. The sleeping rooms were connected with the instruments by cables for transmitting the electrophysiological information. Each person tested was given the opportunity to sleep undisturbed for about 6 hours.

The polysomnograph was used to provide a record of physiological events during sleep on chart paper. A Grass Model 78D EEG Polygraph Data Recording System was used. Measurement of oxygen levels in the arterial blood was obtained by means of an Ohmeda BioxIII Pulse Oximeter. Polysomnography is a procedure during which

different physiological variables during sleep may be recorded by means of the electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (chin EMG).

Standard electrode placements were used for EEG recording: central electrodes C_3/A_2 and C_4/A_1 and occipital electrodes O_2/A_1 and O_1/A_2; the chin EMG measured the electrical activity of the muscle. Two EOGs measured REM sleep. A_1 and A_2 were reference electrodes.

Brain-wave activity recorded for these areas was used to determine the sleep state. The record of eye-movement was obtained by measuring the potential difference between the back and the front of the eye. Eye movement between electrodes generates voltage potentials because the retina is electronegative with respect to the cornea. The particular placement of the electrodes allowed the detection of vertical as well as horizontal eye movements.

The most frequently used site to detect generalized skeletal muscle activity, namely the muscles on the chin (the mental, submental and diagastric muscles) were used. In addition, respiration was recorded and oxygen levels in the blood were measured. To monitor respiratory efforts and airflow, movements of the chest and abdomen and airflow of the nose and mouth, respectively, were

recorded. Oxygen levels were measured using a probe placed on the ear or finger whereby the amount of light absorbed by tissue indicated oxygen saturation. Signals were amplified and recorded on a polygraph set to a chart speed of 15 mm/second. Sleep records were scored in 20-second epochs according to standardized criteria set forth by Rechtschaffen and Kales (1968).

Sleep latency testing to measure excessive sleepiness was performed by utilizing the multiple sleep latency test (MSLT). This test consisted of five 20-minute naps every 2 hours. In our study, we assumed characteristic findings in narcolepsy during daytime polysomnography to be sleep latencies of less than 10 minutes, typically below 5 minutes, with at least two sleep-onset REM periods (REM appearing within 20 minutes after sleep onset). During all-night polysomnography, the same findings are frequently seen (International Classification of Sleep Disorders, 1990). To ensure proper interpretation of these findings, the patients were allowed no access to drugs which influence sleep for at least 14 days prior to testing. Nocturnal polysomnography is recommended in the night preceding MSLT to diagnose sleep disorders which could mimic the features of narcolepsy. Finally the results were

analyzed to see whether practical guidelines for screening for narcolepsy could be offered to psychiatric practitioners.

C. RESULTS

C.1 Subjects

C.1.1 Inclusion Criteria

From October 1990 through July 1991, 489 patients were either admitted to the Psychiatric Ward at the University of Alberta Hospitals or seen for the first time in Dr. Hays' general psychiatric practice. They were scrutinized to see if they had an hallucinating psychosis and, if they did, whether this disorder met DSM-III-R criteria for schizophrenic disorder (American Psychiatric Association, 1987). Thirty patients were included in this way.

C.1.2 Exclusion Criteria

Eight patients had a family history of major psychosis in a first-degree relative, and 2 were adopted and the biological parents unknown.

- 6 patients had abused drugs or alcohol shortly before the onset of their hallucinations.
- 3 patients were found to have brain damage

Eleven patients remained and their characteristics are set out in the case summaries which follow and are displayed in Tables IV-VI.

TABLE IV: PATIENT CHARACTERISTICS

			Symptoms			
Patient Number	*Sex*	*Age*	*Catap.*	*Naps*	*H/H Halluc.*	*Sleep Paralysis*
1	F	19	+	+	+	
2	F	23		+	+	
3	M	33	+	+	+	+
4	F	17	+	+	+	+
5	F	39		+	+	
6	M	50			+	+
7	F	18		+	+	+
8	F	35		+	+	+
9	F	31	+	+	+	+
10	F	24	+	+	+	+
11	M	38	+	+	+	+

Catap. = Cataplexy

H/H Halluc. = Hypnagogic/Hypnopompic Hallucinations

Naps = periods of sleep during a day lasting approximately 10-20 minutes

+ = present

TABLE V: TESTS DONE

Patient Number	*Tests Done*	*Analeptics Used*
1	Patient refused investigation	Y
2	Patient refused investigation	N
3	MSLT on drugs; Full study: physician refused	N
4	MSLT on drugs; Full study: patient and physician refused	N
5	MSLT on drugs; Full study: patient refused	Y
6	MSLT on drugs; Full study: physician refused	N
7	MSLT on drugs; Full study: physician refused	N
8	Full sleep study with MSLT; drug-free	N
9	Full sleep study with MSLT; drug-free	Y
10	Full sleep study with MSLT; drug-free	Y
11	Full sleep study with MSLT; drug-free	Y

MSLT = Multiple Sleep Latency Test; Y = Yes; N = No

TABLE VI: RESULTS OF TESTS

Pat. No.	*Results of MSLT while on drugs*	*Polysom. (drug-free)*	*MSLT (drug-free)*	*Response to analeptics*
1				Partial effect at low dose
2				
3	SL 5.4 min; no REM			
4	SL 10.7 min; no REM			
5	Did not sleep			Negative
6	SL 13.0 min; no REM			
7	Slept in one nap; no REM			
8		SL 13.6 min; REML 153.0 min	SL 10.2 min; no REM episodes	
9		SL 25 min; REML 98.0 min; OSA 67% O_2	SL 15.0 min; 2 REM episodes	Positive
10		SL 9.0 min; REML 61.0 min	SL 10.4 min; 3 REM episodes	Positive
11		SL 3.7 min; REML 59.3 min	SL 3.0 min; 2 REM episodes	Positive

MSLT = Multiple Sleep Latency Test

Polysom. = Polysomnography

SL = Sleep Latency

REML = REM Latency

OSA = Obstructive Sleep Apnea

C.2 Case Summaries

C.2.1 Case Number 1

Nineteen year old woman, admitted with the diagnosis of schizophrenia. Her first symptoms were auditory hallucinations which had started in her early teens. She also had hypnagogic hallucinations, sleep attacks and cataplexy. She refused any investigations, feeling comfortable with her auditory hallucinations. Her hallucinations diminished at once when she received dextroamphetamine and the first day this drug was administered was also the first hallucination-free day she had experienced for several years.

C.2.2 Case Number 2

Twenty-three year old female, admitted with the diagnosis of schizophrenia. Presented symptoms were auditory hallucinations. She also had excessive daytime sleepiness with refreshing naps and hypnagogic hallucinations. The patient refused to have any tests done and was not given analeptics.

C.2.3 Case Number 3

Thirty-three year old male admitted with the diagnosis of schizophrenia, depression and obsessive compulsive disorder. Onset was with sleep paralysis. He had the full tetrad of narcolepsy with symptoms starting in childhood. MSLT was done while the patient was on medications and showed sleep latency (SL) of 5.4 minutes but no REM. No further investigations were done due to his physician wanting to continue his current medications.

C.2.4 Case Number 4

Seventeen year old female admitted with the diagnosis of psychotic depression. The onset was with auditory and visual hallucinations, and during daytime the patient had microsleeps and naps. She had the full narcoleptic tetrad. MSLT performed while on medications showed sleep in all naps, a mean SL of 10.7 minutes and no REM. Neither her physician nor she wished to proceed with further tests.

C.2.5 Case Number 5

Thirty-nine year old female with a diagnosis of schizophrenia. Onset was with auditory hallucinations at the age of 24. She had hypnagogic hallucinations and

excessive daytime sleepiness with naps. At the time of investigation, she was taking neuroleptic medications which she did not wish to discontinue. MSLT done while she was on medications failed to show sleep in the naps despite her hypersomnia.

C.2.6 Case Number 6

Fifty year old male admitted with the diagnosis of schizophrenia. He experienced symptoms of auditory and visual hallucinations and depression. Onset was with hypnagogic hallucinations. Later he developed sleep paralysis. An MSLT done while the patient was on medications showed an SL of 13.0 minutes and no REM. His physician did not wish to stop treatment, so further investigations were not conducted.

C.2.7 Case Number 7

Eighteen year old female with the diagnosis of schizophrenia. Onset was with sleepiness. She had daytime sleepiness, sleep paralysis and hypnagogic hallucinations. An MSLT performed while she was on medications did not show any REM. Further investigations were not carried out because her physician did not wish to interrupt her course of antipsychotic medication.

C.2.8 Case Number 8

Thirty-three year old female, admitted with the diagnosis of schizophrenia. The onset was with auditory hallucinations which began a few years before admission. She also had hypnagogic hallucinations, excessive sleepiness with refreshing naps and sleep paralysis. Nocturnal polysomnography showed an SL of 13.6 minutes and an RL 153.0 minutes. An MSLT showed SL 10.2 minutes and no REM.

C.2.9 Case Number 9

Thirty-one year old obese female admitted with the diagnosis of psychosis. Onset was with mainly visual hallucinations. She had the full narcoleptic tetrad. Nocturnal polysomnography revealed obstructive sleep apnea (OSA) with maximal oxygen desaturation of 67%. An MSLT showed a SL of 15.3 minutes with episodes of REM in 2 naps. The diagnosis of narcolepsy was based on the patient's history and MSLT test. She became asymptomatic on 100 mg of dextroamphetamine daily.

C.2.10 Case Number 10

Twenty-four year old female, admitted due to depression and psychosis. She had the full tetrad of narcolepsy. Diagnosis of her narcolepsy was made on the

basis of history and MSLT. Polysomnography showed an SL of 9 minutes and an RL of 61 minutes. The MSLT a showed SL of 10.5 minutes with sleep onset REMs in 3 naps. She improved on dextroamphetamine but remained depressed.

C.2.11 Case Number 11

Thirty-eight year old male, admitted with the diagnosis of schizophrenia. He had auditory hallucinations and was paranoid and deluded. He had the full narcoleptic tetrad starting with an "image" at the age of 7. He was diagnosed as narcoleptic on the basis of his history, but also his laboratory testing was typical of narcolepsy (SL < 5 minutes; REM in 2 naps). Polysomnography showed an SL of 3.7 minutes and an RL of 59.3 minutes. The MSLT showed mean SL of 3.9 minutes with REM in 2 naps. He became asymptomatic within 24 hours on dextroamphetamine.

C.3 Overview of Case Summaries

As reference to Tables III, IV and V will show, all of the above 11 patients had hypnagogic or hypnopompic hallucinations.

- 8 had sleep paralysis
- 10 had attacks of sleep

- 6 had cataplexy
- 4 had 3/4 of the tetrad, and usually cataplexy was the missing member
- 5 had the complete tetrad
- 2 had no investigations done
- In 5, the only investigation was an MSLT while they were still taking antipsychotics and other medications
- 4 had complete nocturnal polysomnography and an MSLT while drug-free; 3 of these had narcolepsy confirmed

D. DISCUSSION

Of the 30 patients originally included in this inquiry, 3 proved to have narcolepsy confirmed by both clinical and MSLT measures, and this proportion (10%) is in accord with the estimated percentage proposed by Douglass and his associates (Douglass *et al.*, 1991).

MSLT and nocturnal polysomnography are tests which are mainly useful in relation to the diagnosis of narcolepsy when cataplexy is absent. If cataplexy and sleep attacks are both present, sleep-onset REM is so regularly found (Kales *et al.*, 1987) that the tests are almost superfluous. On these grounds, if we assess the incidence by clinical criteria, 6 of the 11 are found to have narcolepsy (patient numbers 1, 3, 4, 9, 10, 11). Six out of 30, is of course, 20%, which substantially exceeds the estimated incidence offered by Douglass *et al.* (1991).

If we confine our attention to the 11 patients who remained when those of the 30 who had a family history of psychosis or a history of substance abuse had been excluded, only 5 remain in whom narcolepsy has not been diagnosed. But in these remaining 5 narcolepsy has not been ruled out. Some patients who did not admit to cataplexy, it transpired, only realized that they had been experiencing cataplexy after it had gone away. Patient number 11, for example, an

educated and intelligent man who gave an excellent account of his symptoms, was slow to acknowledge cataplexy. Eventually, after becoming asymptomatic, he recalled that his upper face would collapse when his favourite sports team had scored, his jaw retained its tone, but his upper face and neck became atonic and his head slumped forward. It follows that there may be some among the remaining 5 who may have had minor variants of cataplexy.

Some symptoms found frequently in narcolepsy are auxiliary. A patient may find himself in places where he had not expected to be, or might put down a cigarette, turn back to it, and find it was burned away; these symptoms may arise in narcolepsy as the consequence of microsleeps - patches of sleep during which activity is maintained but memory is not.

A psychiatrist subscribing to the currently popular concept of dissociative diseases (Andreasen and Black, 1991) might make this diagnosis to account for the auxiliary symptoms. As reference to Putnam's Dissociation Scale (Bernstein and Putnam, 1986) shows, some symptoms regarded by some as diagnostic of dissociative disorder would be regarded by others as diagnostic of daytime drowsiness with microsleeps. But Putnam denies (Dr. P. Hays, personal communication) that a manifestation such as finding himself in a place without knowing how he got there, finding himself

dressed in clothes which he cannot remember putting on, finding new possessions without remembering buying them, and amnesia for events (sometimes important events), may be diagnostic of narcoleptic phenomena, and says instead that these are dissociative symptoms. Andreasen and Black (1991) in their textbook characterize dissociative disorders as disturbances in interpretative functions of identity, memory and consciousness. The dissociative disorders include amnestic states, multiple personality disorder, and depersonalization disorder. In differential diagnosis these authors do not include narcoleptic phenomena as well. It is, therefore, not possible to settle diagnostic disagreements of this kind by discussion and the point remains moot.

Further, 2 of these 5 remaining patients (numbers 7 and 8) had all symptoms except cataplexy. Patient number 7 did not proceed with further testing because her psychiatrist was unwilling to stop her medications for the requisite 2 weeks. Patient number 8 was not on medications, and could proceed to nocturnal polysomnography and MSLT. At nocturnal polysomnography, her sleep latency was 13.6 minutes, and at MSLT it was 10.2 minutes. There was no sleep onset REM. She demonstrated a degree of drowsiness, but not the characteristic REM pattern of narcolepsy. The other 3 of the 5 patients without the complete tetrad,

patients numbers 2, 5 and 6, only had two of the narcoleptic tetrad. Patient numbers 2 and 5 refused further investigation, and the psychiatrist looking after patient number 6 did not wish to proceed further. (MSLT while the patient was still on psychoactive drugs showed an SL of 13 minutes but no REM.) As noted previously, with narcoleptic patients, typical MSLT findings are sleep latencies of less than 10 minutes, often below 5 minutes, and at least 2 sleep-onset REM periods. With only two of the four symptoms present to motivate patient and psychiatrist, it is understandable even to the enthusiast that these participants should have objected to further investigation. (At the same time, in the absence of a family history or a history of substance abuse, these 3 psychoses remain unexplained, and although precise data are not available, complex hallucinations and [especially] sleep paralysis are uncommon in the general population.)

It seems reasonable to conclude that if we exclude from these ranks of hallucinated schizophrenics those with a family history of psychosis in first-degree relatives, and those with a history of substance abuse at or around the onset of the hallucinating psychoses, then about half of the remaining patients (that is, if my findings are

representative, 20% of all hallucinated schizophrenics) are primarily narcoleptic. This is a very surprising conclusion.

D.1 Screening

Let us suppose that the above conclusion is too surprising to credit, and that we prefer to fall back on more conservative estimations of the incidences. There is only one other, that of Douglass *et al.* (1991), who cite 7%.

We may therefore proceed to examine the results further, in order to discover whether they provide any pointers about how to screen psychotic patients for narcolepsy, which is central to the investigation and has proved not to be a trivial question.

The proportion of patients with narcolepsy in a patient sample can be increased by a variety of strategies, and these will now be reviewed: they comprise of clinical, sleep laboratory and genetic and pharmacological strategies.

D.1.1 Clinical Strategies

Whether only a proportion of patients (say those with a negative family history) or all psychotic patients are questioned about the narcoleptic tetrad,

many of the questions asked will be unproductive. This is not an absolute argument against their use: many questions traditionally asked are rarely answered in the affirmative. Questioning does not take long. If it is undertaken carefully, asking about each symptom in several ways, narcolepsy will soon declare itself. A patient may deny sleep paralysis but note that intruders sometimes hold him down in bed or make him helpless with drugs. Hypnagogic hallucinations are often not thought of as abnormal or as relevant, and can take many forms. Habitual nappers do not volunteer that this feature of their lives is a problem, especially since it may be a solution. Cataplexy, as already noted, may be difficult to picture to the patient in such a way that he/she recognizes the topic of the question as congruous with his/her own atonic response to excitement. It may be that the interviewer needs some skill or experience to ensure that clinical screening does not miss too many atypical patients.

The main argument in favour of screening clinically is, perhaps, that it can be done at the very outset. When the patient is first seen, he/she is questioned. All investigations and treatments occur later. If any clinical findings call for withholding symptomatic treatment or for undertaking investigations

which can only be done on drug-free patients, then it is at the outset that they should be elicited. That this is particularly true for hallucinated psychotic patients was clear from the results. All the psychiatrists in the inpatient unit had agreed to let their patients be screened clinically. All psychiatrists were cooperative, personally pleasant, and interested in the research. But in four instances the consultant did not permit sleep investigations to proceed further. The usual reason for this was that treatment had already started and had produced, or promised soon to produce, some benefit. *Primum non nocere* (that is, it is the first duty of the doctor not to harm his patient), and stopping medications carried with it the risk of letting symptoms which had settled recrudesce, or letting symptoms which persisted progress.

If a psychiatrist has a patient with an hallucinating schizophrenic disorder, then he/she will adopt one of two main approaches. He/She will either think that the patient has a syndrome which is not an illness in its own right, and for which a cause must be vigorously sought; or he/she will think that the patient has a Kraepelinian endogenous psychosis. In the first instance, antipsychotic drugs would be

symptomatic remedies; in the second they would be specific, corresponding to vitamin B_{12} for pernicious anaemia (the older term for B_{12} deficiency) or to penicillin for streptococcal infection. In the first instance, the psychiatrist might be willing to withhold symptomatic remedies in case a specific remedy could be provided; in the second, the psychiatrist might understandably protest at withholding a specific so that amphetamines could be given a trial. Even in the first instance, where the approach is most conducive to using the sleep laboratory, symptomatic antipsychotic remedies may have improved the patient's lot, and may make the psychiatrist hesitate to agree to the withdrawal of all drugs for the requisite two weeks. It follows that screening for narcolepsy is a matter of urgency. If clinical screening is the only measure, it must be done before the physician on call has had time to prescribe phenothiazines or tricyclic antidepressants or benzodiazepines. Since these are frequently administered before a patient arrives at the ward, it is apparent that the point at which the narcolepsy questions are asked must be very early indeed.

D.1.2 Sleep Laboratory

It was clear from the outset that getting patients in a drug-free state ready for a full sleep laboratory assessment was going to be difficult to arrange in most instances. The investigation here being reported was always envisaged as a practical one. In this sleep laboratory, narcolepsy is diagnosed more often from the MSLT than from the nocturnal polysomnogram. It was possible that patients given an MSLT even while on drugs might produce enough abnormalities to make the diagnosis of narcolepsy a proper conclusion to draw, and constitute an argument for a full drug-free study. In 5 trials, this hope proved vain: the occasional evidence of excessive drowsiness induced by the medications that patients were taking prevailed. Almost all the drugs in use in psychiatry tend to suppress REM, so that the hope of highly diagnostic findings such as sleep-onset REM was virtually impossible to achieve.

Full sleep studies on drug-free patients must be done early because of the problems associated with stopping current medications. Sleep studies are expensive and should probably not be done on patients with cataplexy and sleep attacks (because that combination is so highly diagnostic) unless treatment

is inexplicably failing. In some countries it may not be permitted to treat patients with cerebral stimulants (analeptics) unless the diagnosis has been supported by laboratory findings. This is both illogical and costly, since a sleep laboratory study costs more than $1,000. Also, in most areas, immediate access to a sleep laboratory cannot be guaranteed, a circumstance which, apart from any inconvenience, increases the risk that the attending doctor or one of his associates will start symptomatic remedies.

Because MSLT is not valid unless the previous night's sleep has been normal for the patient, it must be preceded by a nocturnal polysomnogram. But if MSLT were used (say, on the ward), for screening, then it might be feasible to use it with no more than a nursing log of the preceding night's sleep.

D.1.3 Genetic Studies

HLA typing costs about $300 per patient, but it increases the proportion of identified narcoleptics in a sample. Whether it would be worth using as a screening device depends on the value of a skilled interviewer's time. Probably it would be worth using it on the patients who have narcolepsy without cataplexy or on patients already on medications and

about whom there is some question of the wisdom of stopping medications. It would, in the case of a "positive" finding, increase the confidence of the clinician: most tests are done at least partly for that purpose.

D.1.4 Pharmacological Studies

A therapeutic trial of amphetamines is one of the easiest approaches to screening. The usual response is prompt and convincing. Patient number 1, on whom dextroamphetamine was given a tentative trial, at once had her first hallucination-free day in years (the antipsychotic medications, nevertheless, were not withdrawn; and the patient was, in any case, refusing further investigation). But some doctors and some legislation may not countenance the use of analeptics such as amphetamines in this setting. Beamish and Kiloh (1960) reviewed several cases of psychotic illnesses in which large quantities of amphetamine consumption caused clouding of consciousness with delirious features, excitement, and overactivity of the sympathetic nervous system. In the majority, however, the picture resembled that of paranoid schizophrenia.

Screening, it turns out, is not difficult for the clinician who is convinced that psychosis requires an

explanation and who includes among the explanations he will entertain the concept of a schizophreniform variant of narcolepsy. But early questioning and investigations are paramount, since once the opportunity is lost the ground can be made up only by expensive and worrying backtracking.

E. CONCLUSION

Douglass *et al.* (1991) described the existence of schizophrenic syndromes in narcoleptics which were the consequence of, indeed an atypical expression of, narcolepsy.

The project reported here was designed to study schizophrenic illnesses which were the product of underlying narcolepsy, in order to find the most practical methods of identifying such patients and, by identifying them, to estimate the incidence of this compound state.

Patients were selected by including those with hallucinating schizophrenic illnesses, and then excluding those whose illnesses were associated with antecedents of known etiological importance: that is, the schizophrenic illnesses studied were those for which no causal explanation of even an approximate kind was to found.

Narcolepsy was diagnosed by clinical means (history and mental status) and subsequently, where possible, by sleep laboratory studies (nocturnal polysomnography and MSLT).

Douglass *et al.* (1991) estimated that about 7% of hallucinating schizophrenics are essentially narcoleptic. In the present study, between 10 and 20% of the

hallucinating schizophrenics appeared to be primarily narcoleptic, supporting the proposition of Douglass *et al.* (1991) that the condition was common, and indicating that their estimate of 7% might be conservative.

It followed from the above that narcolepsy is a condition which is well worth looking for in patients with the schizophrenic syndrome.

The present study tended to confirm that sleep laboratory testing could not be done even in a modified form (MSLT alone) when patients were receiving drugs and that stopping drugs for diagnostic tests of narcolepsy was not something which patients or doctors would undertake readily. Because drugs are started so early in a patient's course, and may be instituted in the case (for example) of anxiolytics before the patient is diagnosed, the necessity for a sleep laboratory study must be determined at the very outset of the patient's course. It follows that questioning about the narcoleptic tetrad should be part of the initial history-taking in patients who display schizophrenic syndrome, and that the discovery of the tetrad, or most of the tetrad, constitutes a contraindication to medication until any sleep studies which are called for are contemplated. At the same time one may conclude that for simplicity and economy a drug-free patient could be tested

by performing MSLT on the ward, since this procedure captures most narcoleptics and is more practicable than a full sleep study.

Where narcolepsy is strongly suspected, but medications have been started and it is not feasible, for whatever reasons, to stop them, HLA typing could be used as an aid to diagnosis. Its low specificity makes it as much an aid to the diagnostician's confidence as to diagnostic accuracy. Further, the expense of the procedure is a real drawback in the present financial climate. Its most useful practical application would probably be in patients without cataplexy or in those who, while they were symptomatically narcoleptic, had responded gratifyingly to antipsychotic medications and were thus poor candidates for withdrawal of current drugs and a trial of analeptics.

The last possibility, that of trying analeptics, will probably become a popular auxiliary method of diagnosis. It can be used without stopping other medications, and, if the correct dose is prescribed, the results are prompt. Unfortunately, hallucinating narcoleptics sometimes need doses higher than those usually prescribed in the diagnostic trial of a drug, and inadequate dosage may cause the diagnostician falsely to reject the diagnosis of narcolepsy (personal communication with Dr. P. Hays).

Rejecting narcolepsy prematurely in this way would be a function of lack of confidence in the reality of the diagnosis or the high incidence of the diagnosis which is claimed by Douglass *et al.* (1991) and supported by this study. This leads on to the main overall conclusion which can be drawn from this work and the investigations which preceded it: narcolepsy is there to be found among symptomatically schizophrenic illnesses, but it must be pointedly and specifically sought by the diagnostician at the outset of the relationship, that is, at the first diagnostic interview. This is turn can only be done if the results of the Douglass *et al.* (1991) study and of replications or parallel investigations such as this one, are promulgated and become part of psychiatrists' central body of knowledge. Clinicians do not change their patterns of thought or conduct rapidly if only a publication or two prompt them to do so. A series of studies all pointing in the same direction will alter the thinking of the leaders of the profession, themselves usually conservative and senior, following which the practitioners are more ready to entertain new diagnostic categories. It is therefore to be hoped that other studies of this kind will be performed, and that, if true, the results obtained so far will be both refined and confirmed.

F. REFERENCES

Adams K. and Oswald I. (1977) Sleep is for tissue restoration. J. Royal Coll. Physicians 11: 376-388.

Aldrich M.S. (1990) Current concepts: narcolepsy. New Engl. J. Med. 323: 389-394.

Aldrich M.S. (1991) The neurobiology of narcolepsy. Trends Neurosci. 14: 235-239.

American Psychiatric Association (1987) Diagnostic and Statistical Manual of Mental Disorders - DSM-III-R, Third Edition, Revised, Washington, D.C., pp. 113-118.

American Sleep Disorders Association (1990) The International Classification of Sleep Disorders. Diagnostic and Coding Manual. Allen Press Inc., Lawrence, Kansas, pp. 15-17.

Anch A.M., Browman C.P., Milter M.M. and Walsh J.K. (1988) Sleep: A Scientific Perspective, Prentice Hall, Englewood Cliffs, N.J., pp. 1-8.

Andreasen N.C. (1987) The diagnosis of schizophrenia. Schizophr. Bull. 13: 9-27.

Andreasen N.C. and Black D.W. (eds.) [1991] Introductory Textbook of Psychiatry, American Psychiatric Association, Washington, D.C., pp. 159-160.

Aserinsky E. and Kleitman N. (1953) Regularly occurring periods of eye motility and concomitant phenomena during sleep. Science 118: 273.

Baghdoyan H.A., Lydic R., Callaway C.W. and Hobson J.A. (1989) Neuropsychopharmacol. 2: 67-79.

Beamish P. and Kiloh L.G. (1960) Psychoses due to amphetamine consumption. J. Ment. Sci. 106: 337-343.

Berger H. (1929) Ueber das elektroenkephalogramm des menschen. Arch. Psychiatr. Nervember, 87: 527-570.

Bernstein E.M. and Putnam F.W. (1986) Development, reliability and validity of a dissociation scale. J. Nerv. Ment. Dis. 174: 727-735.

Carskadon M.A. and Dement W.C. (1989) In: Principles and Practice of Sleep Medicine, Lamsback W. (ed.), W.B. Saunders Co., Philadelphia, PA., pp. 30-13.

Carskadon M.A., Dement W.C., Mitler M.M., Roth T., Philip R. and Westbrook S.K. (1986) Guildelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. Sleep 9: 519-524.

Cheney D.L. (1992) Sleep in psychiatric illness. Neurosci. Facts, 3: 1-4.

Dalen P. and Hays P. (1990) Aetiological heterogeneity of schizophrenia: the problem and the evidence. Br. J. Psychiat. 157: 119-122.

Daniels L. (1934) Narcolepsy. Medicine 13: 1-122.

Davis H., Davis P.H., Loomis A.L. Harvey A.L. and Hobart G. (1937) Changes in human brain potentials during the onset of sleep. Science 86: 448-450.

Dement W.C. and Kleitman N. (1957) Cyclic variations in EEG during sleep and their relation to eye movements, body motility and dreaming. EEG and Clin. Neurophysiol. 9: 673-690.

Douglass A.B., Hays P., Pazderka F. and Russell J.M. (1991) Florid refractory schizophrenias that turn out to be treatable variants of HLA-associated narcolepsy. J. Nerv. Ment. Dis. 179: 12-17.

Douglass A.B. and Hays P. (1987) Three simultaneous major sleep disorders. Can. J. Psychiat. 32: 57-60.

Freemon F.R. (1972) Sleep Research: A Critical Review. Charles C. Thomas, Springfield, Ill., pp. 3-48.

Gelineau J. (1880) De la narcolepsie. Gaz Hop (Paris) 53: 626-628.

Gelineau J. (1880) De la narcolepsie. Gaz Hop (Paris) 54: 635-737.

Gillin J.C. (1989) In: Principles and Practice of Sleep Medicine, Lamsback W. (ed.), W.B. Saunders Co., Philadelphia, PA., pp. 425-426.

Gillin J.C. and Wyatt R.J. (1975) Schizophrenia: per chance a dream? Int. Rev. Neurobiol. 17: 297-342.

Guilleminant Ch. (1989) Narcolpesy syndrome. In: Principles and Practice of Sleep Medicine, Lamsback W (ed.), W.B. Saunders Co., Philadephia, PA., pp. 338-346.

Hartmann E. (1973) The Functions of Sleep, Yale University, New Haven, CT.

Hays P. (1984) The nosological status of schizophrenia. Lancet i: 1342-1345.

Heller C., Glotzbach G., Grahn D. and Radlene C. (1988) Sleep dependent changes in the thermo-regulatory system. In: Clinical Physiology of Sleep, Lydic R. and Bielbuyck Y.F. (eds.), American Physiological Society, Bethesda, MD., pp. 145-158.

Hobson J.A. (1990) Sleep and dreaming. J. Neurosci. 10: 371-382.

Hytell J. (1982) Citalopram - pharmacological profile of a specific serotonin uptake inhibitor with antidepressant activity. Prog. NeuroPsychopharmacol. & Biol. Psychiat. 6: 278-291.

Jenkins J.B. and Dallenbach K.M. (1924) Obliviscence during sleep and waking. Am. J. Psychol. 35: 605-612.

Kales A., Bixler E.O., Soldatos C.R., Cadieux R.J., Manfredi R. and Vela-Bueno A. (1987) Narcolepsy/cataplexy. IV: diagnostic value of daytime nap recordings. Acta. Neurol. Scand. 75: 223-230.

Kales A., Bixler E.O., Soldatos S.R., Cadieux R.J., Manfredi R. and Vela-Bueno A. (1987) Narcolepsy/cataplexy. IV. Diagnostic value of daytime nap recordings. Acta Neurol Scand. 75: 223-230.

Kales A., Vela-Bueno A. and Kales J.D. (1987) Sleep disorders, sleep apnea and narcolepsy. Ann. Int. Med. 106: 434-443.

Kraepelin E. (1971) Dementia Praecox and Paraphrenia, Barclay R.M. (trans.), Krieger Publishing Co., New York, N.Y., pp. 5-73.

Krueger J.M., Walter J. and Levin C. (1985a) Induction of slow-wave sleep by interleukin-1. In: The Physiologic, Metabolic and Immunologic Actions of Interleukin-1. Alan R. Liss, New York, pp. 161-170.

Krueger J.M., Walter J. and Levin C. (1985b) Factor S and related somnogens: an immune theory for slow-wave sleep. In: Brain Mechanisms of Sleep, McGinty D.Y. (ed.), Raven Press, New York, pp. 253-275.

Kryger M.H., Roth R. and Dement W.C. (1989) Principles and Practice of Sleep Medicine, W.B. Saunders Co., Philadelphia, PA.

Lishman W.A. (1987) Organic Psychiatry: The Psychological Consequences of Cerebral Disorder, Blackwell Scientific Publications, pp. 617-626.

McGaugh J.L., Gold P.E., Van Buskirk R.B. and Haycock Y.W. (1975) Modulating influences of hormones and catecholamines on memory storage process. In: Hormones, Homeostasis and the Brain, Gispen W.H., Van Wimershom-Greidanus T.B., Bohus B. and de Wied D. (eds.), Elsevier, Amsterdam, pp. 151-162.

McGinty D.J., Harper T.M. and Fairbanks M.K. (1974) Neuronal unit activity and the control of sleep states. In: Advances in Sleep Research, Vol. 1, Weitzman E. (ed.), Spectrum Pub., New York, pp. 173-212.

Meddis R. (1977) The Sleep Instinct. Routledge and Kegan Paul, London.

Mikulincer M., Babkoff M.H., Caspy T. and Sing H. (1989) The effects of 72 hours of sleep loss on psychological variables. Br. J. Psychol. 80: 145-162.

Moruzzi G. (1972) The sleep-waking cycle. Ergebuisse der Physiologie 64: 1-165.

Nicholson A.N. and Pascoe P.A.(1989) Rapid eye movement sleep and continuity. Depression and antidepressants. Drugs (1989); 38 Suppl. 1: 4-13; discussion 49-50.

Nutt D.J. and Glue P. (1991) Clinical pharmacology of anxiolytics and antidepressants: a psychopharmacological perspective. In: Psychopharmacology of Anxiolytics and Antidepressants, File S.E. (ed.), Pergamon Press Inc., New York, N.Y., pp. 1-28.

Oswald I. (1974) Sleep, Penguin Press, Harmondworth, Middlesex.

Rechteschaffen A. and Kales A. (eds.) [1968] A Manual for Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. BIS/BRI UCLA, Los Angeles, CA.

Reite M.L., Nagel K.E. and Ruddy J.R. (1990) The Evaluation and Management of Sleep Disorders, American Psychiatric Press, Inc., Washington, London, pp. 127-141.

Reynolds Ch.F. (1989) Sleep in affective disorders. In: Principles and Practice of Sleep Medicine, Lamsback W (ed.), W.B. Saunders Co., Philadephia, PA., pp. 413-415.

Roy A. (1976) Psychiatric aspects of narcolepsy. Br. J. Psychiat. 128: 562-565.

Silverman D.H.S. and Karnovsky M.L. (1989) Serotonin and peptide neuromodulators: recent disorders and new ideas. In: Advances in Enzymology, Meister A. (ed.), Wiley, New York, N.Y., pp. 203-226.

Slater E., Beard A.W. and Clithero E. (1963) The schizophrenia-like psychoses of epilepsy. Br. J. Psychiat. 109: 95-150.

Smith C.M. (1958) Psychosomatic aspects of narcolepsy. J. Ment. Sci. 104: 593-607.

Sours J.A. (1963) Narcolepsy and other disturbances in the sleep-waking rhythm: a study of 115 cases with review of the literature. J. Nerv. Ment. Dis. 137: 525-542.

Storey P. (1986) Psychological Medicine: An Introduction to Psychiatry, 10th Edition. Churchill Livingstone Inc., New York, N.Y., pp. 124-159.

Tennant F.S. and Groesbech C.J. (1972) Psychiatric effects of hashish. Arch. Gen. Psychiat. 27: 133.

Vogel G., Reynolds Ch.F., Akiskal H.S., Lemmi H., Gillin J.C.H., Zarcome V., Joseph K.C., Dubé D., Sitaram N. and Watson R. (1989) Psychiatric disorders. In: Principles and Practice of Sleep Medicine, Lamsback W (ed.), W.B. Saunders Co., Philadephia, PA, pp. 413-430.

Webb W.B. (1975) Sleep: The Gentle Tyrant, Prentice-Hall, Englewood Cliffs.

Wilcox J. (1985) Psychopathology and narcolepsy. Neuropsychobiol. 14: 170-172.

Williams R.L., Karacan I. and Moore C.A. (1988) Sleep Disorders. Diagnosis and Treatment. Wiley & Sons, Interscience Publications.

Wyatt R.J., Alexander R.C., Egan M.F. and Kirch D.G. (1988) Schizophrenia, just the facts. What do we know, how well do we know it? Schizophr. Res. 1: 3-18.

Young D. and Scoville W.B. (1938) Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. Med. Clin. North Am. May: pp. 637-646.

Zepelin H. and Rechtschaffer A. (1974) Mammalian sleep, longevity and energy conservation. Brain Behav. Evolut. 10: 425-470.